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The DRI Development Process: Issues Related to Extrapolation and Interpolation

Developed by:
Stephanie A. Atkinson, PhD
McMaster University
Ontario, Canada

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Background Paper

The DRI Development Process: Issues Related to Extrapolation and Interpolation

Stephanie A. Atkinson, PhD [1]

Abstract

The methods of extrapolation or interpolation are employed in setting dietary standards when direct measures are not available for the criteria that form the basis of setting an Estimated Average Requirement (EAR), Adequate Intake (AI) or Tolerable Upper Level (UL) and thus there is a need to derive values from older to younger populations or vice versa. In brief, extrapolation, which might better be described as scaling, involves applying a mathematical model to nutrient recommendations for one age group to another by adjusting the value based on body mass (weight) or surface area either in a linear fashion or to an exponent that takes into account metabolic differences between the age groups in question. Although the basic concepts of scaling date back to the 1800s, there is not yet universal agreement on the best methods to employ when extrapolation is required to estimate dietary reference values and the methods employed are not consistent between nutrients. The populations for which such methods are frequently employed are infants and children owing to the paucity of relevant research data available. When extrapolating values for children down from those of adults, a weight or metabolic factor with adjustment for growth is often employed. Values for young children may also be extrapolated up from infants; values for adults may be extrapolated up from children or values for older adults may be extrapolated up from young adults. Extrapolation and interpolation methods should only be applied when sound scientific data are severely lacking, and in such cases the method should be modeled with a consistent and clearly elucidated approach. The latter will require application of internationally accepted standards for growth, body size, body composition, and inclusion of appropriate adjustments for physiological differences between age groups (metabolic efficiency, weight change, or physical activity). This paper reviews the methods of extrapolation employed in the USA/Canada reports on Dietary Reference Intakes and the nutrients affected.

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1. Introduction

Definitions of adjustments to derive reference intake values

The method of extrapolation is employed in setting nutrient-based dietary standards when relevant age-specific direct experimental data are not available for the criteria that form the basis of setting an Estimated Average Requirement (EAR), Adequate Intake (AI) or Tolerable Upper Level (UL). In brief, extrapolation, which might be better described as scaling, involves applying a mathematical model to nutrient recommendations, in this case the EAR, AI or UL as required, for one age group to another by adjusting the value based to a function of body mass (weight) or surface area to an exponent that takes into account metabolic differences between the age groups in question or energy intake. The populations for which such methods are frequently employed are infants and children owing to the paucity of relevant research data available in this age groups. When extrapolating values for children down from those of adults, a weight or metabolic factor with adjustment for growth is often employed. Values for young children may also be extrapolated up from infants; values for adults may be extrapolated up from children or values for older adults may be extrapolated up from young adults. While extrapolation based on indicators of average body size or metabolic turnover is widely used in existing dietary standard reports, one must be cognizant of the inherent errors particularly for those nutrients which are deposited in significant amounts in tissues during growth, such as amino acids, calcium, iron and others.

Extrapolation methods are also often required when setting nutrient recommendations for older adults by scaling values for younger adults. Although this usually employs only a direct adjustment for reference body weights between the two age groups, it does not account for age related differences in absorption or excretion of nutrients owing to degenerative processes, metabolic rate or activity levels. As evidence is emerging that such factors indeed change with advanced aging, future extrapolation models should adjust for their influence in deriving nutrient recommendations for older populations.

As an alternative to extrapolation, the method of interpolation has been employed in dietary standards from other countries, usually in the instance of deriving values from younger and older age groups.

Each of the extrapolation methods will be discussed in detail with examples and note of their limitations.

Models of extrapolation

Extrapolation/scaling between age groups

For many nutrients, sufficient research of direct measurements on large groups of subjects is not available that allow for derivation of requirements for every age group and gender. This is particularly true for older infants (7 months to 2 years) and for children of pre-school and school ages, and for the elderly. While both in adults and children the nutrient supply needs to cover not only the requirements for maintenance metabolism, but also obligatory losses and physical activity, children, in addition, have high and specific energy and nutrient needs for growth. These

are particularly large during rapid growth in infancy, the preschool growth spurt and the pubertal growth spurt [1]. In the recent review of agency/country reports of dietary recommendations [2], it appeared that the variability in recommendation for specific nutrients in children may have been a consequence of differences in concepts about the best methodological approach to use, and in the way the theoretical approaches were applied rather than real physiological and environmental differences between populations [3].

The concepts of "scaling" to adjust for physiological differences between groups of varying body size can be traced historically back to the finding in 1883 of Rubner [4] that in dogs of various sizes (3-31 kg) the basal metabolic rate (oxygen utilisation and heat production) increased as total body weight decreased, but that there was a constant linear relationship between body surface area and metabolic rate. This finding was extended to different species (of different body weight) in 1910 by Voit [5]. Because there is also a regular relationship between body surface area and body size within a species [5,6] it can be concluded that that the basal metabolic rate is also a function of body weight. Log-log plots of body weights of different species (e.g. mouse to elephant) versus metabolic rate gave a line with a slope of about 0.75 and an intercept (coefficient) independent of the species [7-9]. From the literature on pharmacokinetics it is apparent that there are similar allometric relationships between renal elimination, hepatic blood flow and hepatic enzyme activities across species with body weight to the power of 0.67-0.75 (10), while resting energy expenditure within a species with a wide range of possible body size (1-100 kg) like the dog shows an exponent of 0.64 to body weight and is close to the theoretical surface area value of 0.67 [11]. This exponent value may be dependent on body size [12], a question which has yet been investigated in man with a >25-fold range of possible body weights and which can not be resolved by comparisons between species. Moreover, and possibly quantitatively more important, age/maturation specific studies of absorption, elimination, distribution and metabolism per nutrient are needed. It is highly unlikely that different nutrients are similarly related to metabolic rate.

Each method of extrapolation reported in use with dietary reference standards will be discussed below with details of the extrapolation equations included..

a) Scaling based on body size

Nutrient requirement may be estimated using an extrapolation or scaling model between ages based on body weight or mass taken to the power of 1.0 (linear) using age and gender appropriate reference body weights. The first step is to establish appropriate population reference weights and heights, which may vary between country/agency reports to reflect the stature and weight of the racial mix of the country(ies) for whom the dietary standard is developed. The approaches used to develop reference body weights are provided in a later section of this paper.

Assuming there is no knowledge of an association between metabolic rate and nutrient requirement, a generic mathematical model based on body weight may be employed such as:

$$\textit{Calculated reference intake}_{age}$$

$$= \textit{adult reference intake} \times (\textit{representative weight}_{age} / \textit{representative weight}_{adult})$$

A major limitation of this approach is that it does not allow for variations between age groups in intermediary metabolic rates, energy intake, or basal metabolic rate. This approach will consistently produce lower nutrient intake values than values based on body surface area or metabolic body weight.

An example of extrapolation of an EAR/AI up from younger adults for older adults vice versa was accomplished using reference body weights using the following equation:

$$EAR/AI_{younger\ adults} = EAR/AI_{older\ adults}\ x\ (F)$$

$$F = weight_{younger\ adults}/weight_{older\ adult}$$

Exceptions to the use of body weight in extrapolating Adequate Intakes (AI) from the AI for adults to an AI for children occurred for water, potassium and sodium. In these instances, energy intakes rather than body weight were used in the extrapolation equations (see below) because high levels of physical activity are associated with increased losses of electrolytes in sweat. The energy intake values represented the average of median energy intakes for both genders for each age group based on data from NHANES. In the case of extrapolating the AI for sodium for older adults from that for younger adults, it was also based on the combined average of median energy intakes for men and women based on the NHANES III data, since energy intake declines with age. The equation employed is:

For water, potassium and sodium [13], extrapolation down from AI for adults to an AI for children

$$AI_{child} = AI_{adult}\ x\ (F)$$

$$Where\ F = (Energy\ Intake_{child}/Energy\ Intake_{adult})$$

For sodium [13] only, the extrapolation up from younger adults to older adults was adjusted for combined median energy intakes for men and women following the equation:

$$AI_{older\ adults} = AI_{younger\ adults}\ x\ Energy\ Intake_{older\ adults}/Energy\ Intake_{younger\ adults}$$

b) **Scaling based on metabolic turnover**

When appropriate data are not available to determine a nutrient requirement or upper level of intake for younger to older age groups, such as infants to young children, estimates have been derived by employing an exponent value to body mass, which adjusts for metabolic differences related to body weight [14,15]. This method assumes that the maintenance needs of the nutrient, expressed with respect to metabolic weight, are similar for adults and children. Such metabolic scaling does not include an adjustment for growth because it is based on a value for a growing infant (see further discussion of adjustments for growth below).
The problem with this method is that there is a lack of consensus on the adjustment factor that best reflects *basal metabolic rate* (BMR).Various exponent values to estimate BMR have been

proposed over the past centuries including metabolic body mass as body mass$^{0.66}$ [4], or as body mass$^{0.75}$ [7,14]. The choice of the exponent to be used in the calculation of metabolic body mass remains controversial and is in the range from 0.6 to 0.8 [15, 16-18]. Thus, nutrient reference intake values can be estimated based on different approaches of estimating metabolic body mass such as:

$$Calculated\ reference\ intake_{age} = adult\ reference\ intake\ x$$
$$(representative\ weight_{age}\ /representative\ adult\ weight)^{0.66}$$

or

$$Calculated\ reference\ intake_{age} = adult\ reference\ intake\ x$$
$$(representative\ weight_{age}\ /representative\ adult\ weight)^{0.75}$$

Either of these models will produce higher reference intake values for children than those based on body mass. The assumption inherent in this method is that the maintenance needs of the nutrient, expressed with respect to metabolic weight are similar for adults and children.

An example of extrapolation of AI values from younger (0-6 mo) to older (7-12 mo) infants is:

$$AI_{7\text{-}12\ mo} = AI_{0\text{-}6\ mo}\ x\ (F)$$

$$F = (weight_{7\text{-}12\ mo}/weight_{0\text{-}5\ mo})^{0.75}$$

With respect to the Tolerable Upper Intake Level, in most instances primary data were not available to establish an UL for children. In this case, the UL for adults was extrapolated down using reference body weight $^{0.75}$ for all nutrients except sodium, and in this case median energy intake was used in the adjustment equations. The respective equations employed are:

$$UL_{child} = UL_{adult}\ x\ Weight_{child}/Weight_{adult}$$

For sodium the extrapolation equation was:

$$UL_{child} = UL_{adult}\ x\ Energy\ Intake_{child}/Energy\ Intake_{adult}$$

c) Scaling based on relative body surface area

If one uses *relative body surface area*, which shows some correlation to basal metabolic rate, as the adjustment factor to account for metabolic differences between adults and children, then the generic mathematical model is:

$$Calculated\ reference\ intake_{age} = adult\ reference\ intake\ x$$
$$(representative\ body\ surface\ area_{age}\ /representative\ body\ surface\ area\ adult)$$

This method of calculation will result in higher relative nutrient reference intake values than those based on body weight, being almost two-fold higher in the case of infants under 1 year of age [2].

Interpolation method

In the DRI reports, the interpolation method was not employed. An example of the application of the interpolation methods is found in the PRI report for the European Community provided by the Scientific Committee for Food [19]. For infants aged 6-11 months, the values were derived by interpolation between those for infants below 6 months which are often derived from intakes of breast fed infants, and those calculated for the 1-3 years group [19].

Accounting for growth in extrapolations from adults to children

Since adults are non-growing, in the situation that nutrient intake values are extrapolated down to growing children as in (b) above, a factor for growth must be added. In the USA/Canada DRI reports, the factor for growth applied for all nutrients was the approximate proportional increase in protein requirements for growth established in the FAO/WHO/UNU report [20]. An example of the equation used and values employed for growth factors follows:

Extrapolation from AI or the EAR for adults to an AI or EAR for children for all nutrients except potassium and sodium

$$(AI) \ EAR_{child} = (AI) \ EAR_{adult} \ x \ (F)$$

$$F = (weight_{child}/weight_{adult})^{0.75} \ (1 + growth \ factor*)$$

* Growth Factors (proportional increase in protein requirements for growth from FAO/WHO/UNU1[20]

Age Group	Growth Factor
7 mo-3y	0.30
4-8 y	0.15
9-13 y	0.15
14-18 y (males)	0.15 (0 for females)

Approaches to establishing reference body weights

A key factor in applying reference body weights in models of extrapolation is that they reflect the population-based standard for the country(ies) for whom the dietary standard is developed. For the initial report of the USA/Canada DRI [21], data were based on heights and Body Mass Index (BMI) collected between 1988-1994 for the Third National Health and Nutrition Examination Survey (NHANES III) in the United States. Using the reported median heights for life stage and gender groups up to age 30, the median weights were computed from the reported median BMI for the same groups. The reference weights of adults age 19-30 were applied to all adult age groups on the assumption that weight should not change at the older ages if activity is maintained. Beginning with the DRI report on Macronutrients (IOM, 2002) [22], the reference weights and heights were updated based on new data on median body mass index and height-for-age data from the Centers for Disease Control and Prevention/National Center for Health

Statistics Growth Charts [23]. At the time the DRI reports were developed there were not reference weights and heights for Canadian populations so they could not be considered.

In instances where dietary standards target multiple countries such as that for the European Community [19], calculations of energy and selected nutrients intakes were based on rounded values for mean body weights and heights of children at different ages, based on pooling national data sets from Belgium, Denmark, France, Germany, Greece, Italy, Spain, the Netherlands and the UK, weighted on the basis of each country's population at any given age. An alternate approach such as in the Finnish report of 1999 [24] and the French report in 2001 [25] is to adopt a reference weight of 70 kg for men and 60 kg for women. However, for the Finnish report [24] mean body weights for children and adolescents were taken from the 1996 Nordic report, which represented a compilation of population weights and heights from the 3 Nordic countries [26]. In some instances, countries like Mexico adopt reference intake values [27] from other country reports but recognize that the Mexican population is shorter than the average of some other populations and thus adjust the values for reference weights and heights of the Mexican population [27].

Options for use of reference weights and heights:

With the recent publication of the new WHO growth standards as an international reference [28], perhaps this growth reference could be universally adopted for infants and children between 0 to 5 years of age. In North America, for children beyond 5 years of age, data from the 2002 reference growth curves from the National Center for Health Statistics can be used to derive a standard weight and height [23]. For adults, the average weight of men and women at 18 years of age may be used throughout the adult years rather than reflecting the typical secular increase in body weight with age. However, this approach has two limitations. First, many adults have already become overweight or obese by the end of the second decade. Second, with a wide range in adult heights, a "healthy" BMI can be achieved over a wide range of body weights. Perhaps BMI should be used as the adjustment factor. Clearly, this aspect of applying body weight in extrapolation models requires a great deal more attention.

Approaches to extrapolation employed in global dietary standards
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The nutrients for which extrapolation models were employed in the DRI reports of the USA and Canada [13, 22, 30-32], the age groups and model employed for extrapolation are summarized in Tables 1 and 2. As is apparent, the DRI values for infants beyond 6 months and children were frequently derived from extrapolation models. For adults, the estimated average requirement reflects maintenance needs only. In situations where an AI was set for adults (not an EAR), then the value for the AI for adults was substituted for EAR in the equations and an AI was calculated and no RDA was set.

In a recent review [2] of methods of extrapolation employed in setting dietary standards for other countries or agencies, it was noted that only meager specific information was provided on the methodology in most reports. For example, in the D-A-CH (Germany, Austria, Switzerland, Slowenia) Reference Values for Nutrient Intakes [33], the method of extrapolation/ interpolation was only alluded to in the statement, "in those frequent cases in which recommendations could

not be made for every age group, values for intermediate age groups had to be interpolated. For the reports that provided details of methods employed, a summary can be found in Table 5 of the recent review paper (2).

Summary

In the preparation of the USA/Canada DRI reports the lack of relevant data upon which to derive evidence-based population reference intakes for children and youth forced the panels towards the application of models of extrapolation for setting recommended intakes and upper intake values from values established for adults or for young infants, either based on average data for body weight or body surface area or median population median energy intakes. Such extrapolation approaches have several limitations. The appropriate exponent to apply to body mass or surface area measurements, when extrapolating between age groups and whether this differs across age groups, requires further consideration. Physiological differences between adults and young children, especially at a young age, are both quantitative and qualitative in nature. The direct extrapolation based on body weight applied for establishing upper levels of intake in children by extrapolation from adult values is of particular concern given the known differences in substrate absorption, metabolism, and deposition in tissues during growth, as well as renal or other excretion that may not be a function of body size [28]. Clearly, further refinements in the approaches or further research are essential if extrapolation models continue to be relied on for setting nutrient recommendations.

The optimal solution is to eliminate the need for reliance on methods of extrapolation or interpolation to establish nutrient-based dietary standards. To accomplish this, there is an urgent need for further systematic scientific research to establish adequate data on the physiological nutrient requirements especially for children and adolescents, as well as for older adults. Advances in methodologies that are non-invasive will provide for careful metabolic studies that yield the required information. Such non-invasive measurements include using stable isotope tracer methodology for energy expenditure, amino acid oxidation using stable isotope breath tests for the estimation of amino acid requirements, and turnover of macrominerals (e.g., calcium and magnesium) and trace element (e.g. iron and zinc). Body composition measurements to obtain data on nutrient accretion can be obtained longitudinally using methods such as dual energy x-ray absorptiometry, total body electrical conductivity (TOBEC) or magnetic resonance imaging (MRI).It is incumbent upon the nutrition research community to fill existing gaps in knowledge but the support is needed of both academic institutions and funding agencies. Specifically information is required on internationally applicable physiological data (e.g., on absorption, distribution, deposition, metabolism, excretion of nutrients for different gender & life-stage groups) using state-of-the-science techniques

Extrapolation should always be a second choice, but when used by the rationale or scientific basis for the method chosen should be completely transparent and thoroughly described for each nutrient and life-stage group. It must be recognized that there is likely no one 'correct' method for extrapolation, and scientific judgment will likely be part of the process. In addition, if the extrapolation is based on energy intakes, median body weights or activity levels, which may vary widely among populations, a cautious approach to interpretation of the recommended intake values must be advised.

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Table 1 – Method of extrapolation/scaling applied to derive AI/EAR for vitamins and minerals for which AI/EAR was derived from extrapolations at specific age intervals in the Canada/USA Dietary Reference Intake Reports [13, 22,30-32]. The specific method is indicated by the superscript letter as follows: [a] AI extrapolated up from AI for infants 0-6 months; [b] AI extrapolated down from adults to children adjusted for body weight; [c] EAR extrapolated down from adults or older children to young children adjusted for body weight; [d] EAR extrapolated up from younger adults to older adults; [e] AI extrapolated down from older children to younger children adjusted for body weight; [f] AI extrapolated down from adult values adjusted for median energy intakes; [g] AI extrapolated up from younger adults based on median energy intake. See text for details of mathematical models employed.

Age Group	Vitamins	Macro Minerals	Micro Minerals
7-12 mo	Vit A [a] Vit K [a] Thiamin [b] Riboflavin [a] [b] Niacin [b] B-6 [a] [b] Folate [a] [b] Pantothenate [a] [b] Biotin [a] Choline [a]		Iodine [a] Manganese [b] Molybdenum [a]
1-3 yr	Vit A [b] Thiamin [b] Riboflavin [b] Niacin [b] B-6 [b] Folate [b] Pantothenate [b] Biotin [a] Choline [b] Vitamin C [c] Vitamin E [c]	Calcium [e] Magnesium [c] Potassium [f] Sodium [f]	Chromium [b] Copper [c] Molybdenum [c] Selenium [c]
4-8 yr	As for 1-3 yr	Magnesium [c] Potassium [f] Sodium [f]	As for 1-3 yr
9-13 yr	As for 4-8 yr	Potassium [f] Sodium [f]	As for 4-8 yr
14-18 yr	As for 4-8 yr	Potassium [f] Sodium [f]	Chromium [b] Copper [c] Iodine [c] Molybdenum [c] Selenium [d]

			Selenium [d]
31-50 yr	Vitamin C [d] Vitamin E [d]		
51-70 yr	Vitamin C [d] Vitamin E [d]	Phosphorus [d] Sodium [g]	Iodine [d] Copper [d] Molybdenum [d] Zinc [d] Selenium [d]
> 70 yr	Vitamin C [d] Vitamin E [d]	Calcium [h] Phosphorus [d] Sodium [g]	Iodine [d] Iron [d] Copper [d] Molybdenum [d] Zinc [d] Selenium [d]

Table 3 - Macronutrients for which AI/EAR was derived in all or part from extrapolations in the Canada/USA Dietary Reference Intake Report [22] for infants and children are indicated by a √

Age Group	Carbohydrate	Fibre	Protein	Energy
0-6 mo				√
7-12 mo			√	√
1-3 yr	√	√	√	√
4-8 yr	√	√	√	√
9-13 yr	√	√	√	√
14-18 yr	√	√	√	√